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Automatic Determination of Left- and Right-Hand Bone Age in the First Zurich Longitudinal Study

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Key Words
Bone age · Skeletal maturation · Normative data · Greulich-Pyle · Bilateral symmetry

Abstract
Background/Aims: A more advanced bone age (BA) has been reported for the left hand relative to the right hand, while another study has found no such effect. The aim was to study the average difference of automated BoneXpert BA determination (left- vs. right-hand) for normal children, examine the precision of automatic BA and provide a BA reference for normal Caucasian children. ***Methods:*** Radiographs of both hands (age range: 2–20 years) were digitised and analysed automatically to determine Greulich-Pyle BA, producing analysis results for 3,374 left-hand and 2,752 right-hand images. ***Results:*** Comparison of left- and right-hand BA showed no average difference (<0.07 years, 95% confidence). The SD of the differences between left and right sides was 0.25 years for boys as well as girls, implying the precision of automated Greulich-Pyle BA determination was 0.18 years or better. Greulich-Pyle BA for boys and girls were on average 0.10 and 0.21 years below the chronological age. ***Conclusion:*** The left and right hand give the same BA on average and the SD between the sides is 0.25 years, indicating an excellent precision of the automated method.

Introduction

The First Zurich Longitudinal Study (1ZLS) is unique because it involved normal children who were followed with annual X-rays of both hands and yearly measurements from birth to the chronological age (CA) of 20 years – or until final height if the participants were still growing at CA 20 years. The children and the study methods of the 1ZLS have been extensively characterized in many publications [1, 2]. The films of the 1ZLS have now been digitised. This paper is part of a series of reports on the analysis of these digital images using an automated method for determination of bone age (BA) and bone growth. It reports on the basic properties of automated Greulich-Pyle BA and is organised according to the following aims:

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(1) to test the hypothesis that the left and the right hand yields the same BA on average for normal children;
(2) to determine the standard deviation (SD) of the differences between BA determinations in the left and right hands as a function of gender and age, and to use this to estimate the precision of automated BA, and
(3) to report reference values for automated Greulich-Pyle BA for normal Swiss children born around 1955.

Regarding the first aim, we intend to study the average signed difference between left and right BA, which we will sometimes refer to briefly as 'the average difference'. This is to be distinguished from the average absolute difference between the two sides. The motivation for studying the signed difference rather than the absolute difference is that for more than 50 years there has been controversy regarding the average difference (i.e. the average signed difference) between left- and right-hand BA. Roche [3] found that the left hand was more advanced than the right hand, while Baer and Djrkatz [4] found no such effect. In Roche et al. [5], there are 18 references to papers studying this difference. Furthermore, the signed difference has clinical importance: some clinics believe that there is – or could be – a difference, and standardise on one of the sides. Conventionally the left hand is used, but Zurich University uses the right hand. If we can demonstrate that there is no difference, the interpretation of clinical data from various centres would be greatly facilitated and clinicians would no longer have to doubt a BA image taken on the other hand than is customary at their clinic. Additionally, the signed difference can be studied reliably by averaging over many subjects, whereby the precision errors on the BA determination tend to cancel out.

Studying the average absolute difference could also be interesting, but we have not found a statistically sound method to do so: the challenge is that the precision error of the BA method is confounded with this quantity.

Methods

The X-rays of the 1ZLS were recorded at ages 1, 3, 6, 9, 12, 18 and 24 months, and then yearly, until the height gain was less than 0.5 cm per 2 years. Ninety-four percent of the annual images were taken within 2 weeks and 99% within 1 month of the child's birthday. The children were born between January 1954 and February 1956 and were selected randomly within the first 2 weeks after birth. Unfortunately the images taken at the youngest ages, typically below 4–6 years, were so deteriorated that they could not be read by the computer or manually.

The scanning included the 232 children that have been described in numerous previous studies on 1ZLS [2]. Only 3 X-rays were available in one of these children, who was therefore excluded, leaving 119 boys and 112 girls. All the acceptable left- and right-hand images of these children were scanned, giving a total of 6,649 images. The scanning was performed in 300 dpi with 12 bits per pixel with a Vidar Diagnostic Pro Advantage scanner (Vidar, Hemdon, Va., USA) using TWAIN 5.2 software. For this analysis, 9 images which were not taken within 3 months of the child's birthday were excluded, and images above CA 20.25 years were also excluded. One image with an obviously wrong ID label was revealed by applying the automated method and was excluded.

The digital images were processed with the automated method BoneXpert Version 1.0 (Visiana, Holte, Denmark). The methodology has been described in Thodberg et al. [6]; briefly, it computes BA from the radius, ulna and 11 short bones (RUS) in rays 1, 3 and 5. In order to obtain the best compatibility between the automated method and the current Greulich-Pyle BA practice, a multi-centre/multi-rater study was performed to define a transformation of BoneXpert's intrinsic BA into 'BoneXpert Greulich-Pyle BA', which agrees on average with current practice. The participating centres were in Rotterdam and Tübingen, and X-rays from these two centres were rated by one of five raters in order to average out any idiosyncrasies of individual raters [7–9].

The intended Greulich-Pyle BA range of the automated method is 2.5–17 years for boys and 2–15 years for girls. Images are automatically rejected by the method if they lack similarity to its internal models of bone morphology. In the present study, rejections were in all cases due to poor radiographic quality or images below the intended BA range, with the exception of one good quality X-ray within the intended age range which was rejected. 3,374 left-hand images and 2,752 right-hand images were recognised successfully. Due to the above-mentioned decay of the earliest images, there were few images available in the lowest age range (fig. 1). Over 48% of the maximum of 231 images per year of age were available from CA 5 years for the left hand and from CA 8 years for the right. In the CA range of 10–18 years, an average of 96% of the maximum of 231 images for either hand were available in total. The number of right-hand images with a matching left-hand image was 2,704.

Statistics

For the automated BA method, the re-rating precision error on a digital image is exactly zero. The precision error of the entire physical determination of BA is, however, not zero, i.e. repeating the X-ray exposure and analysing it would in general yield a different result. In order to estimate this precision error, we considered the spread of the differences between the left and right hands.

The observed variance of the difference was modelled as being composed of two variance components: two times the precision variance (i.e. the total measurement uncertainty) of the automated BA method and a genuine difference in BA of the two hands.

The observed SD of the differences between left and right BA can thus provide an upper limit on the precision error of BoneXpert BA. The precision error is defined as the SD on a single measurement, i.e. the upper limit of the precision is given as the average SD of all the differences divided by $\sqrt{2}$.

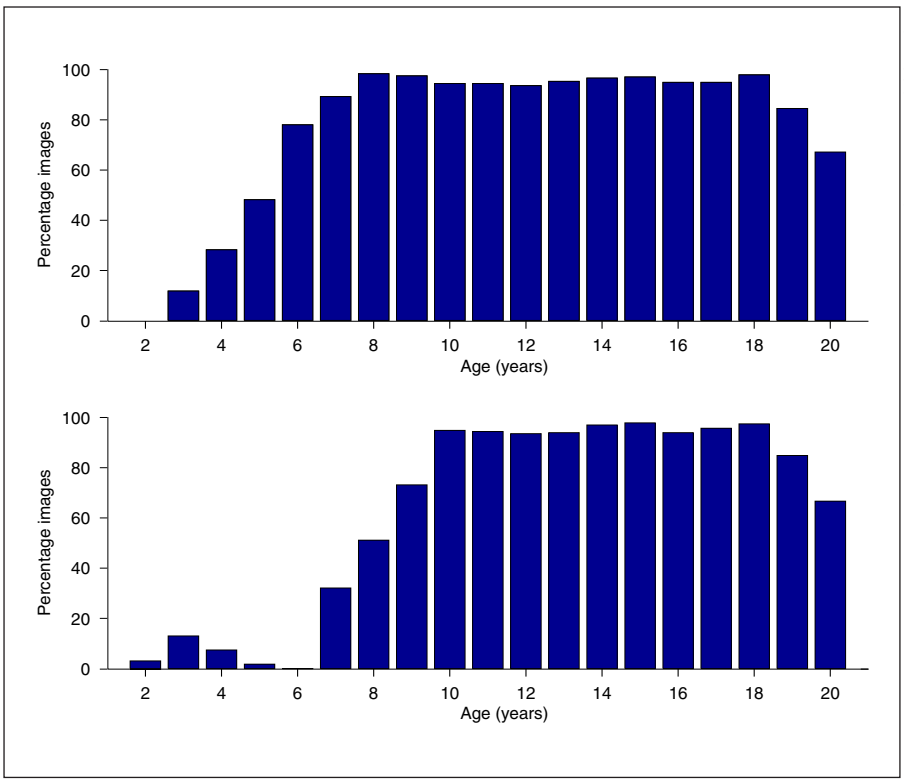

Fig. 1. The upper bar diagram shows the percentage of children with a BoneXpert analysis of the left hand done at each birthday. The lower diagram shows the same for the right hand.

Results

Symmetry

For the 2,704 images with both left- and right-hand BA at the same visit, figure 2 shows the difference between left- and right-hand BA versus the average of the two. The difference appears to be symmetric around zero. The average difference for boys was 0.02 years (95% CI: –0.03 to 0.07), where the CI was computed assuming 119 independent observations. Assuming 1,400 independent observations would lead to a 3–4 times tighter CI. The most correct CI would lie somewhere in between the two, so the quoted interval can be considered conservative. For the girls, the average difference was –0.01 years (95% CI: –0.06 to 0.04).

Precision

The SD of the differences between the sides was dramatically larger above CA 17 and 15 years for boys and girls, respectively. Above these ages, the maturity indicators in the short bones are very poor, and since the automated method was designed to always compute bone as the average BA of all 13 RUS bones, its BA becomes unreliable at these high BAs. Excluding these regions (in accordance with the intended use of the automated method), the SD of the difference was 0.25 years for both sexes. This implies an upper limit of precision of 0.18 years (95% CI: 0.174–0.180).

Reference Data

Figure 3 shows the difference between BA and CA versus CA, with a solid line joining the means of successive CA bins. The average BA retardation for boys and girls was 0.10 and 0.21 years, respectively, when computed over the range CA 3–17 and 3–15 years. There were deviations from this average retardation in some regions, for instance girls aged 9–13 years were retarded by 0.46 years, while BA and CA were the same, on average, at 14–15 years.

The SD of the differences between CA and BA for boys and girls was 1.02 and 1.08 years, respectively, when computed at each age and averaged over the intervals CA 7–17 and 7–15 years, respectively; the SD was considerably smaller below 7 years.

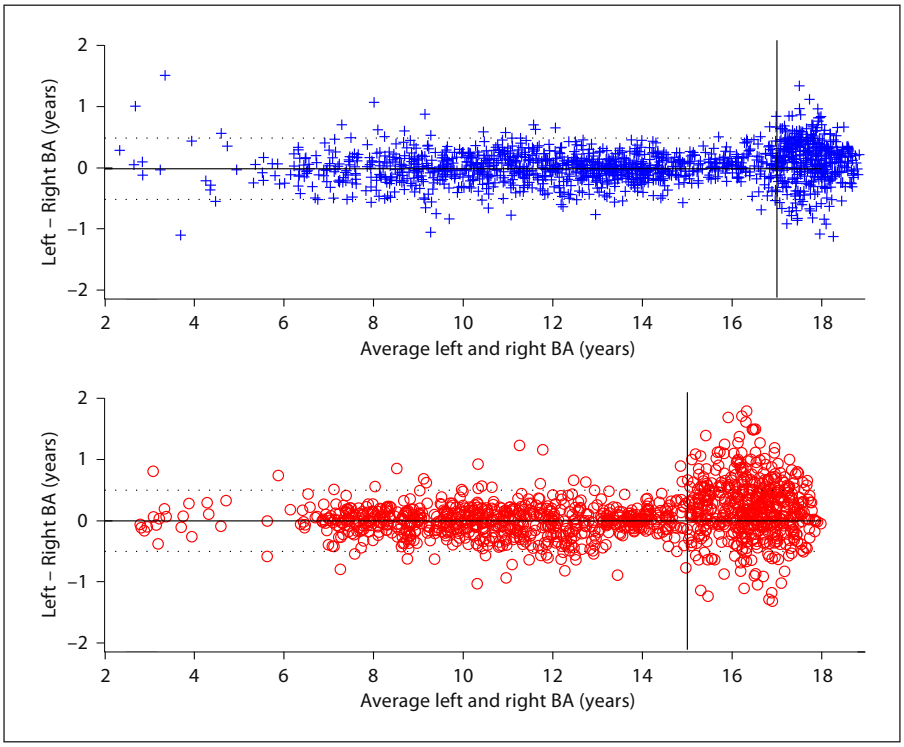

Fig. 2. The difference between BoneXpert BA determined on the left and the right hand shown for each sex vs. the average of the two determinations (boys: upper diagram, girls: lower diagram). The vertical lines at 17 and 15 years indicate the upper limits of the region used to determine the SD and the average difference. The dotted horizontal lines represent ± 2 SD.

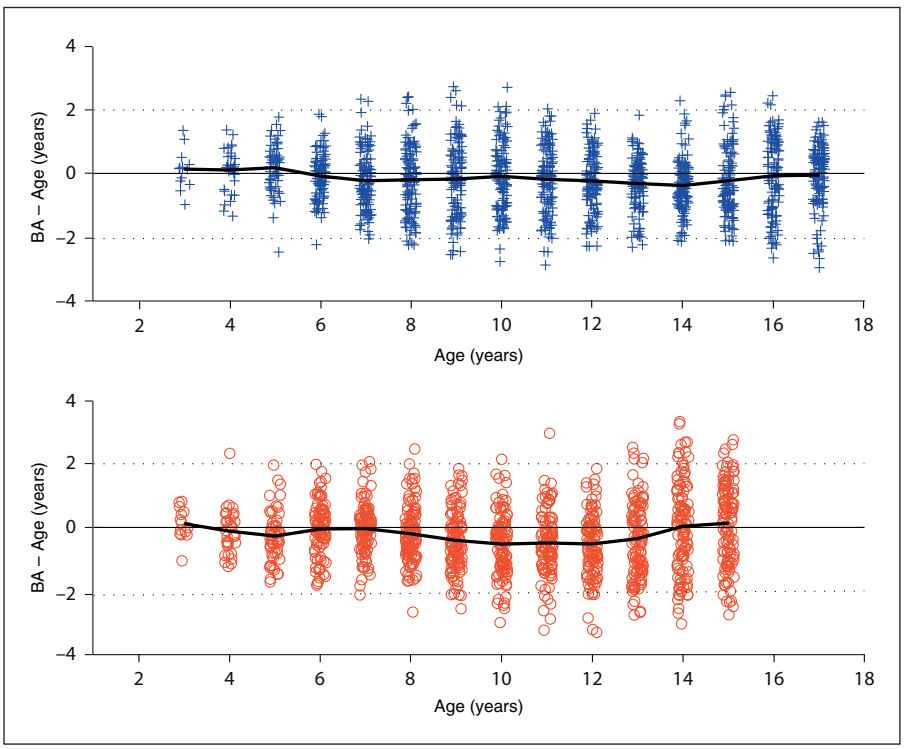

Fig. 3. The difference between BoneXpert BA and CA at each age for boys (upper diagram) and girls (lower diagram). The curve results from joining the mean differences of successive CA bins. The CA values on the x-axis have been jittered for better visibility.

Discussion

Symmetry

Our finding that there was no average difference between the BA of the left and right hands confirms the finding of Baer and Djrkatz [4] and refutes the findings of Roche [3]. The handedness of the 231 children is not known, but since the subjects were randomly selected, approximately 10% can be assumed to be left-handed [10]; therefore, it can be concluded that, on average, the dominant hand appears to mature at the same tempo as the non-dominant hand. Here, 'on average' means averaged over many subjects. BoneXpert determines the length of 10 short bones (the 5 metacarpals; PP1, 3 and 5; and MP3 and 5) and calculates an average length of these 10 bones. On average, the bones grow 4% per year and BoneXpert can measure their size with a precision of 0.7%. The average bone length of the right hand is only a little greater on average, 0.2% for boys and 0.5% for girls. Thus, size and maturity are extremely well related as far as the left and right side of the same individual is concerned.

Precision

As explained in Martin et al. [8], BoneXpert's Greulich-Pyle BA is a non-linear function of bone morphology and, like human raters, is expected to be more precise during phases of rapid morphological change. This is seen clearly in girls where the SD of the differences between left and right is smaller at 13–14.5 years.

The precision of manual BA rating has traditionally been studied as the re-rating precision error, whereby widely different results ranging from 0.25 years [11] to 0.82 years [12] have been found, corresponding to the different reliability of human raters. Unlike manual rating, BoneXpert BA rating is only subject to a between-image precision error since, being based on an entirely deterministic process, its within-image precision error is exactly zero. Using the procedure described above, we found the upper limit on its between-image precision error to be 0.18 years. The uncertainty on this upper limit was extremely small. This result is in good agreement with the upper limits of 0.17 years from Thodberg et al. [6] and 0.17 years from Martin et al. [13], found by a different approach based on longitudinal data series to study BoneXpert's BA rating precision.

Reference Data

The reference data show the skeletal maturation of Swiss children born 1954–56 to be in very good agreement with the population used by Greulich and Pyle, with an average BA retardation of only 0.15 years. The subjects of the 1ZLS developed faster than the healthy Danish subjects studied in 1966 [6], who were found to be 0.70 years behind Greulich-Pyle. Boys and girls showed the same offset within studies in accordance with the view expressed in Tanner et al. [14] that girls and boys in a given population can be expected to have approximately the same BA retardation.

This data could serve as a reference for BoneXpert Greulich-Pyle BA for normal children in Central Europe if it can be assumed that the secular trend from 1960–70 to today is negligible.

Conclusions

BA ratings of the left and right hand showed no average bilateral asymmetry. The mean SD of the difference between left and right hand BA was found to be 0.25 year. This yields an upper limit on the precision of automated BA of 0.18 year. Swiss boys and girls were found to be retarded by 0.10 and 0.21 year relative to BoneXpert Greulich-Pyle BA, respectively.

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Disclosure Statement

The corresponding author is the owner of Visiana, which holds and markets the BoneXpert medical device for automated determination of BA.

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